Hereditary or Acquired Angioedema?

How testing can help you differentiate

With similar clinical presentations, the several forms of angioedema can be hard to differentiate. Advanced Diagnostic Laboratories (ADx) at National Jewish Health offers a unique breadth and depth of testing for angioedema.

Differentiation of Hereditary Angioedema (HAE) and Acquired Angioedema (AAE) Type I, II and Type III

Laboratory Test	Type I HAE	Type II HAE	Type III HAE	Type I AAE	Type II AAE
C1-INH function	Usually Low	Usually Low	Normal	Usually Low	Usually Low
C1-INH level	Usually Low	Normal or elevated	Normal	Usually Low	Normal
C4 level	Usually Low	Usually Low	Normal	Usually Low	Usually Low
C1q level	Normal	Normal	Normal	Usually Low	Usually Low
C1-INH AutoAb	Not usually present	Not usually present	Not usually present	Not usually present	Often present

ADx Comprehensive Angioedema Test Menu

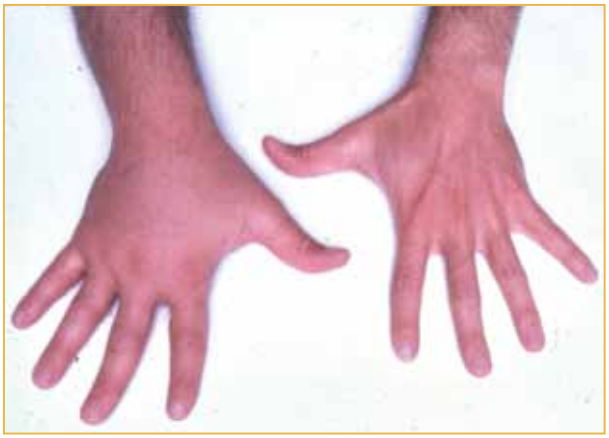
(ADX test code)

- C1-INH Level (CEIQ)
- C1-INH Chromogenic Function (CEICHR)
- C4 Level (C4L)
- C1q Level (C1Q)
- C1-INH Autoantibody (CEIQAP)
- Factor XII Genotyping, C1032G/A
- C1q Autoantibody (C1QAP)

For more information please call the Complement Lab at 303.398.1541

More Sensitive C1-INH Function Test (C1-esterase inhibitor function)

A sensitive test previously available only in Europe has recently been released in the US. The ADx Complement Lab has pioneered use of this method for direct measurement of C1-INH function. The substrate used for the assay is cleaved by the enzyme C1s and generates a colored compound that can be easily detected and quantified. If active C1-INH is present in the patient's serum, less color is produced so the assay directly measures C1-INH function. The chromogenic assay has a broader range of measurement, providing better differentiation of borderline function and more confidence in the high and low ends of the test. A review of the chromogenic assay by Wagner-Bos et al. was published in 2008. The authors analyzed blinded testing from over 15 labs in Europe, and concluded that the assay was worthy of recommendation ***"as a good assay for making a correct diagnosis based on its high sensitivity, clear distinction, and low variability."***



Differentiation of AAE Type II

Type II AAE includes patients who have developed auto-antibodies that react with C1-INH. These antibodies can be measured by an ADx in-house ELISA method.

Genetic Differentiation of HAE Type III

This recently described Type III form of HAE is characterized by classic HAE clinical presentation, except for completely normal C1-INH levels and function. ADx offers a genetic screen for the C1032G/A SNP described by Konrad Bork and colleagues (Bork et al, 2009).

Differentiation of HUVS (Hypocoplementemic Urticarial Vasculitis Syndrome)

Patients with this syndrome usually have auto-antibodies reactive with the collagen-like region of the C1q molecule, and can develop angioedema. These antibodies can be measured by an ADx in-house ELISA method.

Continued Commitment to Advancing Angioedema Testing

ADx is working to develop additional testing for HAE

HAE Type II

- Development of the efficient sequencing of the full length C1-Inhibitor gene for genetic screening

HAE Type III

- Development of a cost effective screen for most or all of the Factor XII gene for additional gain of function mutations that may be linked to HAE Type III.
- Development of a test to pick up the ability of FXIIa and/or Kallikrein to escape control by C1-INH in these patients.

Unique Testing for Chronic Urticaria

ADx also offers testing by flow cytometry for autoantibodies to CD203c. Approximately 40% of patients with chronic urticaria have antibodies to the high affinity IgE receptor (FcεR1) caused by an autoimmune reaction. Patients with this form of autoimmune urticaria have functional IgG antibodies directed against FcεR1 found on mast cells and basophils, which can trigger degranulation. Presence of this autoantibody causes upregulation of the CD203c protein, which is an ideal biomarker.

Anti-FcεR1 measurement is:

- An activation marker for identifying chronic hives
- A marker to monitor response to therapy

Further Reading:

- Zuraw, BL. Clinical practice. Hereditary angioedema. *N Engl J Med.* Sep 4 2008;359(10):1027-1036.
- Zuraw, BL. Diagnosis and management of hereditary angioedema: an American approach. *Transfus Apher Sci.* Dec 2003;29(3):239-245.
- Zuraw, BL, Herschbach, J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol.* Mar 2000;105(3):541-546.

References:

- Bork, K, Wulff, K, Hardt, J, Witzke, G, Staubach, P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol.* Jul 2009;124(1):129-134.
- Wagenaar-Bos, IG, Drouet, C, Aygoren-Pursun, E, et al. Functional C1-inhibitor diagnostics in hereditary angioedema: assay evaluation and recommendations. *J Immunol Methods.* Sep 30 2008;338(1-2):14-20.
- Bowen, T, Cicardi, M, Farkas, H, et al. Canadian 2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema. *J Allergy Clin Immunol.* Sep 2004;114(3):629-637.